1: J Pharm Sci. 1995 May;84(5):614-8. Links

Effect of compression temperature on the consolidation mechanism of chlorpropamide polymorphs.

Otsuka M, **Matsumoto T**, **Higuchi S**, **Otsuka K**, **Kaneniwa N**.

Department of Pharmaceutical Technology, Kobe Pharmaceutical University, Japan.

The effect of environmental temperature on the compression mechanism of chlorpropamide (CPM) polymorph, forms A and C, was investigated with an eccentric type tabletting machine with two load cells and a noncontact displacement transducer. The temperature of the die was controlled at 0 and 45 degrees C by a thermocontroller. Sample powders (200 mg), which were also controlled at 0 and 45 degrees C by a thermocontroller, were compressed at almost 230 MPa. The tabletting dynamic processes of CPM forms A and C at 0 and 45 degrees C were evaluated by Cooper and modified Heckel analyses. The results suggest that particle brittleness or plasticity was affected by compression at different temperatures. The higher tablet hardness of form A at 45 degrees C was thought to be caused by the increased plasticity of primary particles, whereas that of form C at 45 degrees C was ascribed to the decreased size of the secondary particles.

PMID: 7658353 [PubMed - indexed for MEDLINE]

1: J Pharm Pharmacol. 1989 Oct;41(10):665-9.

Effects of the mechanical energy of multi-tableting compression on the polymorphic transformations of chlorpropamide.

Otsuka M, Matsumoto T, Kaneniwa N.

School of Pharmaceutical Sciences, Showa University, Tokyo, Japan.

The effects of the mechanical energy of tableting compression on the polymorphic transformation of chlorpropamide have been examined. A single-punch eccentric tableting machine with a load cell and a non-contact displacement transducer were used to measure compression stress, distance and energy. An amount of 100 mg of the stable form A or the meta-stable form C of the drug was loaded into the press and the sample compressed with a compression stress of 196 MPa at room temperature (20 degrees C). The compression cycle was repeated from 1 to 30 times. The powder X-ray diffraction profiles of the deagglomerated compressed sample powder were measured to calculate the polymorphic content. The results on forms A and C suggested that both forms were transformed into each other in the solid state by mechanical energy during tableting. The contents of forms A and C reached equilibrium at a constant value above 100 J g-1 of compression energy after more than 10 cycles. After 30 tableting cycles of forms A and C, the contents of A, C and the non-crystalline solid were almost constant at about 45, 25 and 30%, respectively. The compression energies were estimated to be about 500-600 J g-1. From the results it seems that the transformation mechanism of forms A and C during tableting were as follows. The crystal form of A or C was converted to a non-crystalline solid by the mechanical energy, and the solid was then transformed into form A or C.

PMID: 2575141 [PubMed - indexed for MEDLINE]

1: J Pharm Pharmacol. 1991 Apr;43(4):226-31.

Effects of tableting pressure on hydration kinetics of theophylline anhydrate tablets.

Otsuka M, Kaneniwa N, Kawakami K, Umezawa O.

School of Pharmaceutical Sciences, Showa University, Tokyo, Japan.

The effects of tableting pressure on hydration kinetics of types I and II theophylline anhydrate tablets at 95% relative humidity, 35 degrees C, have been studied by using various kinetic equations. Relations between tablet expansion and hydration were studied. Samples of 2 cm diameter tablets (1 g) were compressed at 5, 10 and 20 MPa. The hydration of types I and II tablets decreased with increased tableting pressure. The time required for 50% hydration of 2 cm diameter tablets, compressed at various pressures suggests that the tablet hydration rate was affected by the tableting pressure. Types I and II tablets expanded 11.37-16.75% in volume during hydration to the monohydrate. The thickness expansion of the tablets exceeded the diameter expansion as the tablet structure was not uniform owing to the orientation of particles during the compression. The final expansion ratio of the tablets increased with increased tableting compression pressure. The Hancock Sharp constant (m) and fitting of the kinetic data to a suitable model suggested that the hydration of theophylline anhydrate tablets followed the two-dimensional phase boundary equation (type I tablets) or the three-dimensional phase boundary equation (type II tablets).

PMID: 1676732 [PubMed - indexed for MEDLINE]

1: J Pharm Pharmacol. 1983 May;35(5):269-74.

Links

The effects of polymorphism, particle size and compression pressure on the dissolution rate of phenylbutazone tablets.

Tuladhar MD, Carless JE, Summers MP.

The dissolution rate of phenylbutazone from tablets after disintegration has been used to determine whether the drug particles underwent crushing or bonding during compression. Two polymorphic forms of the drug were used and the predominant effect for high drug concentration (60%), during compression was dependent upon the original particle size of the drug and its polymorphic form. With a low drug concentration (10%) in the tablet, the diluent protected the drug particles from bonding together. The particle size change of the drug during compression was affected by the nature of the diluent present. Lactose had an abrasive action on Form A phenylbutazone compared with Avicel but had little effect on the more ductile Form B. When the contact time of compression was decreased from 29 to 0.26 s, the 6 microns particles of drug showed less bonding at the shorter time (faster rate of compression) but the effect observed with the larger particles was independent the compression rate.

PMID: 6134792 [PubMed - indexed for MEDLINE]

International Journal of Pharmaceutics, 88 (1992) 261–273

IJP 02926

Physicochemical characterization of a phase change produced during the wet granulation of chlorpromazine hydrochloride and its effects on tableting [1]

Marion W.Y. Wong and Alan G. Mitchell

Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, B C V6T 1Z3 (Canada)

(Received March 17 1992)
(Modified version received 5 June 1992)
(Accepted 8 June 1992)

Key words: Chlorpromazine hydrochloride; Wet granulation; Hemihydrate; Polymorphism; Physicochemical characterization; Tableting; Tablet strength

Summary

Chlorpromazine hydrochloride (CPZ(II)) exhibits severe lamination and capping when compressed. Wet granulation with ethanol and water to form CPZ granules (CPZ(I)-H') significantly improves tableting. The physicochemical properties of CPZ(II) and its granules were characterized using microscopy, powder X-ray diffraction (XRPD), differential scanning calorimetry (DSC), solution calorimetry, gas adsorption/desorption and gas displacement pycnometry. Marked differences were observed in their morphology. Both appeared crystalline under a scanning electron microscope. CPZ(II) appeared as aggregates of acicular crystals, while the granules were seen as smaller cuboid crystals. XRPD indicated that they were distinct phases. The DSC of CPZ(II) using sealed pans with a pinhole showed an endotherm at 188–189°C (melting), while the granules exhibited two additional endotherms at 50–55°C (dehydration) and 134–137°C (solid-solid transition) prior to melting (187–190°C). Significant changes were also observed in the heats of solution and true densities after wet granulation. It was concluded that CPZ(II) undergoes a phase change to a hemihydrate (CPZ(I)-H) on wet granulation but, as received, the granules exist as a partially dehydrated hemihydrate (CPZ(I)-H') Further investigation showed that CPZ(II) is metastable at room temperature and that the fully dehydrated granulation is the room temperature stable form Differences in the physicochemical properties of CPZ(II) and CPZ(I)-H' were accompanied by differences in their compression profiles Tableting behavior was analyzed using an instrumented Manesty Betapress after mixing with 0.5% w/w magnesium stearate and 0.5% w/w talc. Both materials exhibited a high degree of viscoplastic deformation during compression and no difference in their elastic recoveries during decompression Improvements in the tabletability and tablet strength following wet granulation were attributed to changes in lattice structure which facilitated interparticulate bonding on compaction.

Introduction

Chlorpromazine hydrochloride (CPZ), a phenothiazine antipsychotic, makes poor tablets. Significant sticking to the die wall and picking by the punch faces are observed on compaction of pure

Correspondence to. A.G. Mitchell, Faculty of Pharmaceutical Sciences, The University of British Columbia, 2146 East Mall, Vancouver, B C. V6T 1Z3, Canada

[1] Presented in part at the Sixth Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists, Washington, DC, 1991

unlubricated drug, and severe lamination and capping are seen at all compression pressures.

Wet granulation is used by Rhone-Poulenc to improve tabletability but this is not a conventional wet granulation process since no binding agents are used. Preliminary analysis of chlorpromazine hydrochloride and its granules using powder X-ray diffraction and differential scanning calorimetry (DSC) indicated that a phase change had occurred. Under a scanning electron microscope, the morphology of the two forms were significantly different. CPZ polymorphs have not been reported in the pharmaceutical literature. Dorignac-Calas and Marsau (1972), however, reported the isolation of three different crystal forms of chlorpromazine hydrochloride but only documented the single crystal X-ray data of the high temperature stable form. The phase change produced during the wet granulation of chlorpromazine hydrochloride was characterized and differences in the compaction properties of the granules and original crystals were assessed.

Materials and Methods

Chemicals

Chlorpromazine hydrochloride (CPZ(II), lot M-21673) and chlorpromazine hydrochloride granulated with an ethanol : water mixture (80.5 : 22.9 v/v) and dried at 50°C (CPZ(I)-H′, lot AM97) were obtained from Rhone-Poulenc (Montreal, PQ) with the manufacturer's certification. The granulation process used by Rhone-Poulenc to obtain CPZ(I)-H′ is unusual in that no binding agent is used. Both CPZ(II) (100.4% w/w chlorpromazine hydrochloride) and CPZ(I)-H′ (99.9% w/w chlorpromazine hydrochloride) were used as received. CPZ(I)-H′ is a partially dehydrated hydrate from which the remaining water of crystallization can be removed to give a dehydrated form (CPZ(I)) or which takes up atmospheric water to form a hemihydrate (CPZ(I)-H).

Potassium chloride, lithium fluoride, stearic acid, primary octanol, primary butanol, *t*-butanol and chloroform were analytical grade reagents; methanol and chloroform were GC grade (BDH Chemicals, Toronto, ON). Ethanol and absolute ethanol (StanChem, Vancouver, BC), magnesium stearate (Mallinckrodt, St. Louis, MO), Tris (Parr, Moline, IL), and talc (Cyprus, Alpine, AL) were used as received. Glass distilled water was used throughout.

Scanning electron microscopy (SEM)

CPZ(II) and CPZ(I)-H′ were sputter-coated with gold under vacuum in an argon atmosphere and examined in a scanning electron microscope (Hitachi, Model F-570) using secondary electron imaging with an accelerating velocity of 20 kV.

Powder X-ray diffraction (XRPD)

XRPD profiles were obtained using a high-resolution wide-angle X-ray diffractometer (Rigaku D/MAX-2MBX) with scintillation counter. Lithium fluoride was used in a 1:1 ratio by weight to minimize preferred orientation during cell packing and to correct for small fluctuations in the day-to-day intensity response of the instrument. A total sample size of 400 mg was exposed to Ni-filtered CuK_α radiation (40 kV, 20 mA) and scans were conducted over a 2θ range of 5–55°. Data were analyzed using Rigaku software (version 2.4).

SRM 675 (synthetic fluorophlogopite mica) and 640b (silicon) were NBS standards used in the place of lithium fluoride for quantitating changes in the lattice dimensions of CPZ(I) with the absorption of water. Incorporating the NBS standards enabled shifts in peak positions, due to changes in the unit cell, to be differentiated from machine variability and experimental error. Since CPZ is light sensitive, all quantitative work was performed in the dark.

Solid-state NMR

^{13}C-CP/MAS solid-state NMR was performed using a 400 MHz MSL solid-state NMR spectrophotometer (Bruker, Germany) with 90° pulses on the proton of 7.5 μs. A contact time of 80 μs was used and up to 3728 scans were performed per sample at a recycle time of 20 s. Spectra were processed with a line broadening of 100 Hz.

Thermal microscopy

Samples were mounted in an oil-based liquid with a certified index of refraction of 1.532 (Cargille Laboratory, Inc., Cedar Groves, NJ) and centered in the central chamber of a gas-flow heating/freezing system (Fluid Inc.) designed by the U.S. Geological Society (U.S.G.S.). Preheated atmospheric air was circulated uniformly and continuously above and beneath the sample. Vertical gradients were negligible and horizontal gradients were low and easily calibrated. Heating was controlled with the Fluid Inc. U.S.G.S. calibrated trendicator and thermocouple and monitored using a Doric 410A trendicator. Samples of CPZ(II) and CPZ(I)-H′ were viewed under a 480-fold magnification using a polarized light cross-nicols microscope (Nikon) with a Nikon AFX-IIA camera accessory.

DSC

The thermal behavior of the various forms of chlorpromazine hydrochloride was analyzed using a 910 Differential Scanning Calorimeter module interfaced to a Du Pont Series 99 Thermal Analyzer (Wilmington, DE) and the thermograms were recorded on a chart recorder. 3–5 mg samples were accurately weighed directly into standard aluminum open pans, hermetically sealed pans and sealed pans with 0.1–0.2 mm pinholes. The encapsulated sample was scanned at rates of between 2 and 20°C per min under a purified nitrogen atmosphere. Immediately after each endotherm or exotherm, the temperature was held and the sample was reweighed before resuming the scan. The leading edge of each peak was used to determine the transition temperature. Hydrated samples were also cooled to below the freezing point of water using a cooling accessory with liquid nitrogen and scanned under the conditions specified above. A Sartorius thermal controlled infrared moisture balance (Göttingen, Germany) was used to measure the weight loss on drying and to confirm the weight losses observed during DSC as a result of desolvation. Grinding was performed manually using an agate mortar and pestle. A minimum of three trials were performed for each set of experimental conditions.

Ethanol content

The ethanol content of CPZ(I)-H′ was analyzed using a Hewlett-Packard 5840 gas chromatograph (GC) (Mississauga, ON) with a flame ionization detector (FID) interfaced to a Hewlett-Packard 18850A GC terminal. A 25 m × 0.31 mm Ultra-2 fused silica column was used with 0.52 μm 5% phenylmethylsilicone as the bonded phase. CPZ(I)-H′ was dissolved in chloroform and 2 μl was injected in the split mode using a split ratio of 3:1. The temperatures of the injection port, FID and oven were 160, 250 and 60°C, respectively. Helium was used as the carrier gas and a constant flow rate of 1.0 ml/min was maintained.

Solution calorimetry (SC)

A Tronac Isoperibol Calorimeter Model 458 (Tronac Inc., Orem, UT) was used to determine the heats of solution of CPZ(II), CPZ(I), the partially hydrated form of form I (CPZ(I)-H′) and the fully hydrated form of form I (CPZ(I)-H). The bath temperature of 25.000 ± 0.005°C was monitored throughout the study using a Guildline Model 9540 digital platinum resistance thermometer (Smith Falls, ON). 50 mg of each sample was accurately weighed and encapsulated in a sample cell designed by Winnike et al. (1988). All reactions took place in a 50 ml capacity fully silvered vacuum flask at 25°C with a stirrer rotating at 600 rpm. A minimum of five repetitions were performed for each sample using distilled water as the solvent. Dissolution was rapid and complete. Temperature changes during the reaction were monitored with a thermistor bridge system. The calorimeter was interfaced to an Apple II Plus computer through an ADALAB analog-digital converter and accompanying signal amplifier to facilitate data collection and analysis. Signals were calibrated with Tris and checked using potassium chloride. Heats of solution for potassium chloride were 17.00 ± 0.34 kJ/mol compared with a reported value of 17.22 (Lide, 1991).

Solubility and dissolution rates

Excess amounts of CPZ(I) and CPZ(II) were placed in tightly closed glass containers containing 1-octanol, 1-butanol, *t*-butanol or a mixture of

water in *t*-butanol (1 : 19) and rotated continuously while submerged in a water bath maintained at 25°C protected from light. Samples were drawn until equilibrium solubility was reached. Each extract was immediately centrifuged and the supernatant removed, diluted and analyzed using a diode-array spectrophotometer (Hewlett-Packard 8452A) at 256 nm using the Hewlett Packard 89530 MS-DOS UV/Vis computer software program. With each experiment, a new standard curve was constructed having a coefficient of determination between 0.97 and 0.99. Each run was performed in triplicate with an accompanying blank.

Dissolution rate studies were performed using the compression die apparatus for rotational dissolution proposed by Wood et al. (1965). 250 mg of CPZ(I) or CPZ(II) was accurately weighed into the die cavity and compressed using a manual hydraulic press at 113 MPa with a dwell time of 60 s. The assembly was then mounted vertically in a Fisher motor assembly and rotated at 100 rpm in a jacketed glass beaker containing 250 ml of either distilled water or a mixture of water and tertiary butanol. Aqueous buffered solutions over a pH range of 9–11 were also used in an attempt to decrease the dissolution rate and to differentiate between the two forms (pK_a of chlorpromazine: 9.3 (Albert and Serjeant, 1984)). Experiments were performed at 25°C and 2 ml samples were taken at 0, 5, 10, 15, 20, 25, 30, 40, 50 and 60 s. Appropriate dilutions were made of the collected aliquots to yield a final absorbance reading between 0.2 and 0.8 absorbance units and each sample was analyzed using UV spectroscopy as above.

Gas (helium) displacement pycnometry

True densities of the various forms of CPZ were determined using a helium multipycnometer (Quantachrome Corp., NY). 40–60 g samples were accurately weighed directly into the sample cell with tapping and the reference cell (of known volume) was pressurized to 15–17 lb/inch^2 with a known quantity of predried purified helium.

Relative humidity-composition diagram

CPZ(I) obtained by drying CPZ(I)-H′ at 70°C under vacuum in the presence of silica gel was stored at 25°C in desiccators over saturated salt solutions selected to give relative humidities (RH) of 15, 31, 43, 52, 66, 76 and 90% (National Physical Laboratory, 1958). Once constant weight was established, the powders were sealed in the temperature-controlled chamber of a WA measuring station (Rotronic Hygroskop BT) with a combined temperature-humidity probe (Mitchell, 1984). The % RH of the powders was measured at 25°C. Immediately after a constant humidity reading was recorded, the sample was removed from the chamber and a portion of the bulk was accurately weighed into a sealed pan with pin hole and scanned using the DSC. The weight loss after the dehydration endotherm corresponds to the water content of the powder. After equilibration at the various RH values, samples of the CPZ(I) crystals were subjected to XRPD. CPZ(II) did not exhibit significant weight changes when stored at the above humidities. No dehydration endotherm or weight loss was observed when scanned using DSC. Both form I and form II deliquesced when stored under the ethanol-water saturated atmosphere of the granulation mixture.

Tableting

The tableting behaviour of CPZ (form I and form II), CPZ(I)-H′ and CPZ(I)-H was analyzed using an instrumented rotary tablet press (Manesty Betapress) under running conditions using 1PT punches at a turret time of 1.00 s. A detailed description of the instrumented press and analysis system is given elsewhere (Oates and Mitchell, 1989, 1990; Dwivedi et al., 1991, 1992). Magnesium stearate 0.5% w/w and talc 0.5% w/w were used as tableting lubricants. Tablet strength was evaluated using a CT40 commercial tablet strength tester (Engineering Systems, Nottingham) after storage at approx. 23°C and 34% RH for 24 h.

Results and Discussion

Physicochemical properties of CPZ and its granules

Significant differences were observed between the morphology, X-ray diffractograms, thermal behaviour and true densities of CPZ(II) and its granulated forms.

Examination using SEM showed that CPZ(II) consisted of aggregates of large needle-shaped crystals with step-like ridges on its surfaces and angular edges, whereas, after granulation, the powder consisted of smaller composite cuboid crystals with rounded corners and an irregular pattern of indentations on the crystal faces (Fig. 1).

The powder X-ray diffractograms of CPZ(II) exhibited major peaks at 8.5, 15.7, 18.8 (the base peak), 22.3, 22.8 and 25.1 2θ, with minor peaks at 6.3, 10.0, 14.8, 16.0, 16.9, 20.3, 25.7 and 28.1 2θ,

Fig. 1. Scanning electron images of (a) CPZ(II) and (b) CPZ(I)-H′ (magnification, ×2000)

Fig 1(b)

while the major peaks of CPZ(I)-H′ were observed at 5.6, 11.3, 16.8, 19.2, 20.6, 22.6, 23.4, 27.1 and 28.2 2θ (Fig. 2). The diffractograms of CPZ(I)-H (the fully hydrated granules) and CPZ(I) (the dehydrated granules) were qualitatively the same as CPZ(I)-H′. It is apparent that wet granulation with the ethanol-water mixture leads to a phase change where the new crystal lattice, CPZ(I)-H′, is able to take up or lose water molecules without a marked change in the lattice structure (see below).

The peaks of CPZ(II) were narrower and of greater intensity than those of CPZ(I)-H′, CPZ(I)-H and CPZ(I) indicating that CPZ(II) was

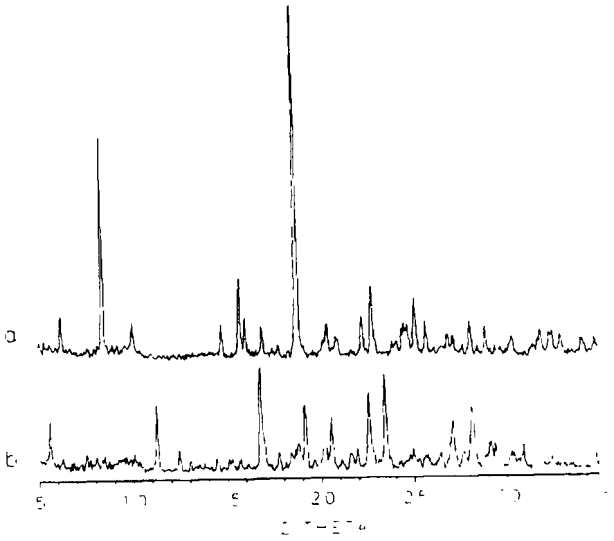


Fig. 2. X-ray diffractograms of (a) CPZ(II) and (b) CPZ(I)-H′ (shown using the same intensity scale for comparison). The diffractograms of CPZ(I)-H and CPZ(I) are qualitatively the same as CPZ(I)-H′

more crystalline. This was confirmed by the sharper, more intense peaks of CPZ(II) obtained from preliminary solid-state NMR studies.

The DSC thermogram of CPZ(II) showed a single melting endotherm at 188–189°C (Fig. 3a), while the thermograms of CPZ(I)-H′ and CPZ(I)-H exhibited two additional endotherms prior to melting – a broad peak due to dehydration and vaporization, and a small endotherm at 132–134°C due to a solid (CPZ(I)) to solid (CPZ(II)) transition (Fig. 3b). Table 1 summarizes the observations made using DSC and thermal microscopy. All transitions recorded on the thermograms were verified by thermal microscopy.

The weight losses when CPZ(I)-H′ and CPZ(I)-H were heated past the first endotherm (70°C) were 1.90 and 2.47% w/w H_2O, respectively. The ethanol content of CPZ(I)-H′ was negligible (0.0144 ± 0.0004% w/v), and the absence of a melting endotherm for water in ther-

TABLE 1

Thermal analysis of CPZ(II) and CPZ(I)-H

Pan type	Scan rate (°C/min)	Peak	Proposed reaction	Temperature [a] (°C)
Thermograms of CPZ(II)				
A, C[b]	10	1	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	188–189
B[b]	10	1	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	184–185
Thermograms of CPZ(I)-H				
A	2–10	1	$CPZ\text{-}H_{(s)} \rightarrow CPZ(I)_{(s)} + 1/2H_2O_{(g)}$	37– 43
		2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	132–134
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	189
B	10	1	$CPZ\text{-}H_{(s)} \rightarrow CPZ(I)_{(s)} + 1/2H_2O_{(g)}$	58
		2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	129
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	187
C	2–10	1	$CPZ\text{-}H_{(s)} \rightarrow CPZ(I)_{(s)} + 1/2H_2O_{(g)}$	50– 55
		2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	134–137
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	187–190
A, C	15, 20	1	$CPZ\text{-}H_{(s)} \rightarrow CPZ(I)_{(s)} + 1/2H_2O_{(g)}$	58
		2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	134–135
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	185–188
Thermograms of CPZ(I)				
A, C	10	2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	135–137
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	187–189
B	10	2	$CPZ(I)_{(s)} \rightarrow CPZ(II)_{(s)}$	134
		3	$CPZ(II)_{(s)} \rightarrow CPZ_{(l)}$	186

[a] Transition temperature measured from the leading edge

[b] A, standard pan; B, sealed pan; C, sealed pan with pinhole

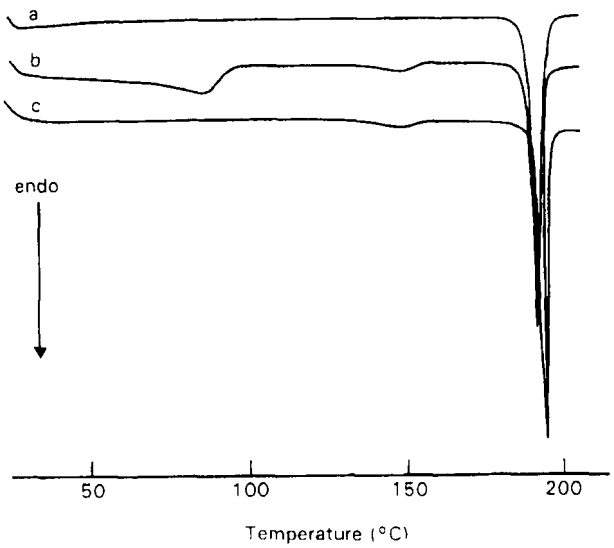


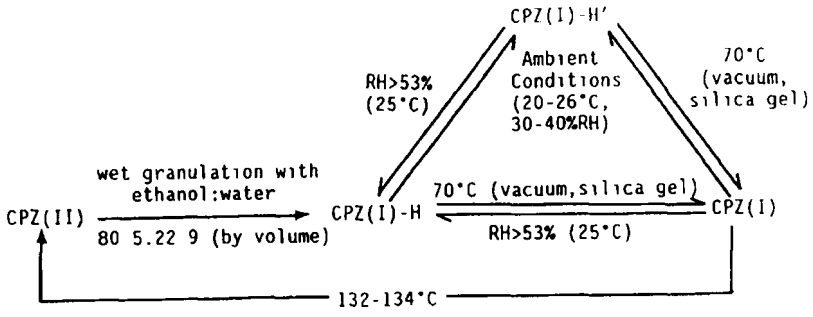
Fig. 3. DSC thermograms of (a) CPZ(II), (b) CPZ(I)-H′ and (c) CPZ(I) using hermetically sealed pans with pinhole.

mograms of CPZ(I)-H′ and CPZ(I)-H when scanned from −30°C indicated that water was present at a molecular level in the crystal lattice.

While the dehydration endotherm disappeared when CPZ(I)-H′ was completely dried at 70°C under vacuum in the presence of silica gel, the second endotherm remained (Fig. 3c). No further weight loss was detected after the second endotherm. Heating past the second endotherm followed by immediate cooling to room temperature and rescanning produced a thermogram identical to that of CPZ(II) (Fig. 3a). The phase change from CPZ(I) to CPZ(II) at elevated temperature was confirmed by XRPD on a sample of CPZ(I)-H′ heated in an oven at 150°C for 10 min. The diffractogram was identical with that of CPZ(II).

The solid-solid transition, confirmed visually using thermal microscopy, suggests enantiotropic polymorphism. Hence by definition, CPZ(II) (i.e., the commercially available chlorpromazine hydrochloride) is a high temperature stable form which must be metastable at room temperature. Dorignac-Calas and Marsau (1972) also reported the existence of a high temperature CPZ crystalline form stable between 147 and 201°C (no preparative details given) compared with the range of 134–189°C found in this work using DSC. However, there was no reverse transition on cooling to below the transition temperature and no evidence of conversion of CPZ(II) to CPZ(I) was found during storage under ambient conditions. When the granulation procedure using the ethanol-water mixture was simulated on a microscope slide and observed under a light microscope, both the presence of liquid and CPZ(II) crystals were found to be necessary for the formation of CPZ(I)-H. It is apparent that while the conversion of CPZ(I) to CPZ(II) occurs at a specific transition temperature on heating, the conversion of CPZ(II) to CPZ(I) only occurs through the intermediary of a hydrate and not through a solid-solid phase change. CPZ(I) (the low temperature stable form) is a dehydrated hydrate in which the hydrate lattice structure does not collapse and recrystallize on removal of the water of crystallization. Scheme 1 summarizes the above.

CPZ polymorphs have not been reported in reviews of the pharmaceutical literature (Wall, 1986; Borka and Haleblian, 1990; Borka, 1991),



Scheme 1. Interconversions of CPZ

and CPZ(I) can be described as a pseudopolymorph since it is obtained by the desolvation process in which the crystal lattice remains intact. This phenomenon was described for cephalexin and cephaloglycin by Pfeiffer et al. (1970) and for calcium gluceptate by Suryanarayanan and Mitchell (1986).

The heats of solution of these forms (Table 2) support the hypothesis that CPZ(II) is a metastable form of chlorpromazine hydrochloride at room temperature and that CPZ(I) is the stable form. The heat of solution for CPZ(I) was higher (more endothermic) than that of CPZ(II). Their true densities were also different. When CPZ(I)-H′ was fully hydrated to give CPZ(I)-H, its heat of solution and true density increased; and when fully dehydrated to give form I, its heat of solution and true density decreased.

Solubility and dissolution studies were performed on CPZ(I) and CPZ(II) in both aqueous and nonaqueous media but no differences were observed in the apparent solubilities of these two forms due to the rapid conversion of CPZ(II) to CPZ(I)-H. Rapid conversion was also observed in the dissolution studies using both buffered and unbuffered aqueous solutions, and a mixture of water and tertiary butanol. The dissolution rates of CPZ(I) and CPZ(II) were virtually identical.

To better understand the hydration/dehydration behaviour of CPZ(I), a relative humidity (RH)-composition phase diagram was constructed (Fig. 4). A typical absorption/desorption isotherm was obtained at RH values between 8 and 53%, and CPZ(I)-H (a stoichiometric hemihydrate) was formed at higher humidities.

TABLE 2

A comparison of the heats of solution and true densities of CPZ(II), CPZ(I), CPZ(I)-H′ and CPZ(I)-H

Material	Heat of solution (kJ mol^{-1})	True density (g cm^{-3})
CPZ(II)	28.80 (0 98) [a]	1 312 (0 001)
CPZ(I)	29.49 (0.24)	1 285 (0 003)
CPZ(I)-H′	34 89 (0.28)	1 299 (0.001)
CPZ(I)-H	35 89 (0.22)	1.304 (0.004)

[a] Mean ± S D ($n = 5$ for solution calorimetry and $n = 6$ for true density measurements)

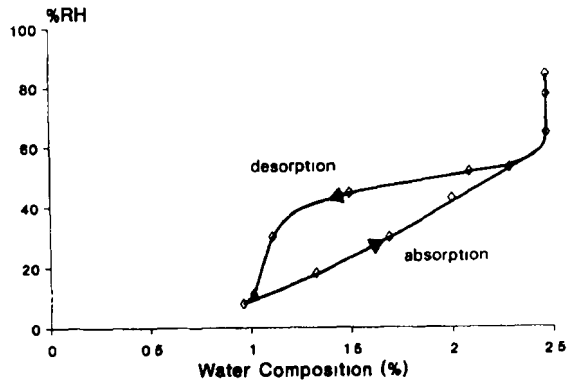


Fig. 4 Relative humidity-composition profile of CPZ(I) (CPZ(I)-H′, as received, contained 1.90% w/w H_2O and CPZ(I)-H contained 2 47% H_2O w/w (0 5 mol H_2O/mol CPZ).

The lattice expansion of CPZ(I) due to the incorporation of water at various RH values was studied using XRPD. A reversible expansion of cromolyn sodium on exposure to water vapor was investigated by Cox et al. (1971). Unlike Cox et al. (1971) who needed to grow single crystals for single crystal diffractometry, we were able to use the single crystal data of Klein and Conrad (1986) for a hemihydrate of CPZ recrystallized from aqueous ethanol. The single crystal data of Klein and Conrad (1986) was converted to a powder pattern using the LAZY PULVERIX program of Yvon et al. (1977). The calculated powder pattern was identical not only with that of CPZ(I)-H but also with that of CPZ(I)-H′ and CPZ(I). Having established that CPZ(I)-H was the same as the hemihydrate reported by Klein and Conrad (1986), we used the lattice parameters of their monoclinic crystal system as the starting point for the indexing and least-squares refinement method of Appleman et al. (1973). The three-dimensional changes in the monoclinic lattice as a function of water content are shown in Fig. 5. While the unit cell gradually expands in the a and c direction with the incorporation of water, the longest length of the unit cell (i.e., along b) contracts. Upon formation of CPZ(I)-H (the hemihydrate) at 2.47% H_2O, expansion in all directions is observed, with the most dramatic increase along b.

Dorignac-Calas and Marsau (1972) isolated a form of chlorpromazine hydrochloride which was

metastable at ambient temperatures with a unit cell volume one-half that reported by Klein and Conrad (1986) for CPZ(I)-H. When the analysis of Yvon et al. (1977) was used to convert the single crystal data of Dorignac-Calas and Marsau (1972) to a powder pattern, the calculated diffractogram agreed with the powder pattern obtained for CPZ(II). CPZ(II) did not form hydrates at any of the RH values tested.

XRPD studies confirmed that the lattices of CPZ(I)-H′ and CPZ(I)-H remained intact after complete dehydration under vacuum in the presence of silica gel at elevated temperatures (70°C) (Fig. 6a). However, at 100°C under vacuum (as above) for prolonged periods of time (i.e., > 3 days), complete conversion of CPZ(I)-H′ to CPZ(II) occurred (Fig. 6d).

Polymorphic transformations have been reported for selected organic substances at high pressures (Drickamer, 1967), and phase changes in pharmaceuticals under compression is not uncommon (Chan and Doelker, 1985). Polymorphic transformations under mechanical stress have also been reported for barbitone (Nogami et al., 1969; Summers et al., 1976), carbamazepine (Lefebvre and Guyot-Hermann, 1986), chloramphenicol (Otsuka and Kaneniwa, 1985, 1986, 1989), chlorpropamide (Otsuka et al., 1989; Matsumoto et al., 1991), indomethacin (Otsuka et al., 1986),

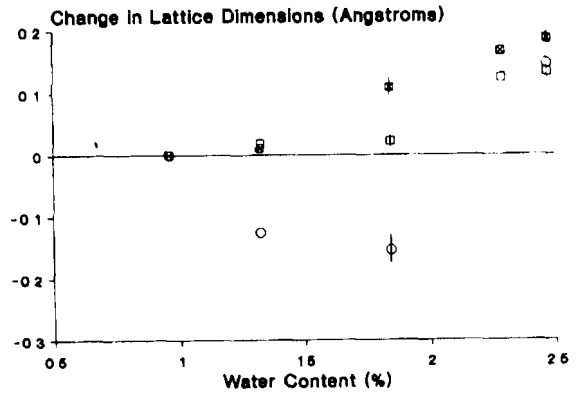


Fig. 5. Changes in the lattice dimensions of CPZ(I) with the incorporation of water. CPZ(I)-H is obtained at 2.47% H_2O (dotted line). Dimensions in the *a* (□), *b* (○) and *c* (⊠) directions are shown. Samples containing 1.85% H_2O were analyzed in triplicate, and the mean and range are provided

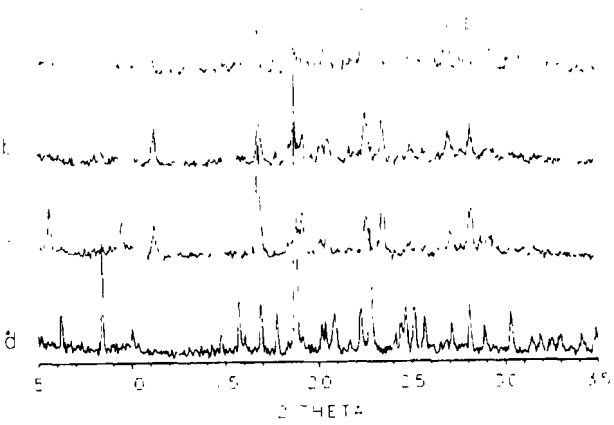


Fig. 6 X-ray diffractograms of CPZ(I)-H′ treated as follows (a) dried under vacuum with silica gel at 70°C; (b) hand-ground and dried as in (a), (c) compressed under 210 MPa (the top face of a tablet was scanned and the appearance of two new peaks at 5.3 and 9.5 2θ are due to magnesium stearate and talc, respectively); and (d) heated under vacuum with silica gel at 100°C Diffractograms (a)–(d) are shown using the same intensity scale for direct comparison

phenylbutazone (Ibrahim et al., 1977) and sulphathiazole (Summers et al., 1976). Hand grinding in an agate mortar (Fig. 6b) or compression up to 210 MPa (Fig. 6c) did not affect the crystal lattice of CPZ(I)-H′.

Tableting

Materials which undergo extensive viscoplastic deformation during compression tend to form good tablets. In our Betapress analysis, peak offset time can be used as an indication of the extent of viscoplastic deformation (Oates and Mitchell, 1989; Dwivedi et al., 1991). The peak offset times of CPZ(II) were slightly shorter than for CPZ(I)-H′ (Fig. 7). This difference is unlikely to account for the poor tabletability of CPZ(II) since, compared with other materials, its peak offset times are still relatively long and on this basis alone, CPZ(II) might be expected to form good tablets.

The water of hydration appears to play a role in the particle deformation mechanism during compression and in interparticulate bond formation. Thus, the length of the peak offset times shows that CPZ(I)-H deformed more during compression than CPZ(I). No significant differences

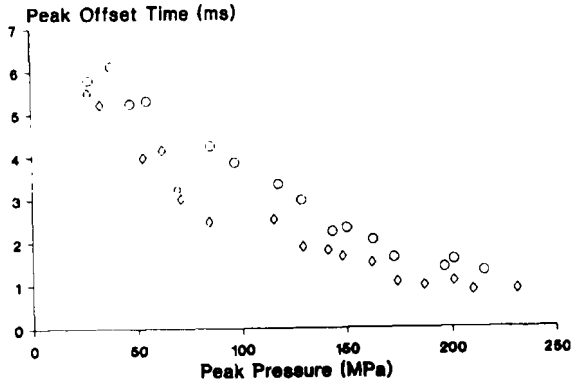


Fig. 7. Peak offset times of CPZ(II) (◇) and CPZ(I)-H′ (○) with increasing compression pressures.

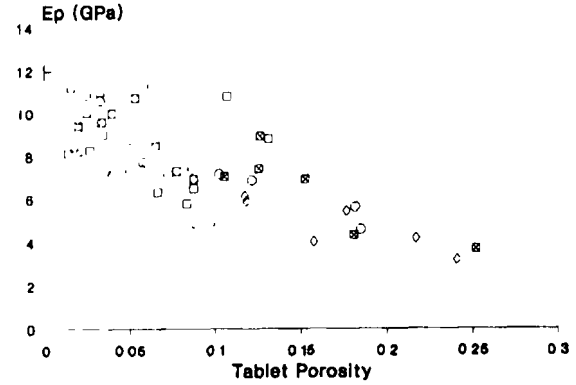


Fig. 9. Elastic recoveries of CPZ(I) (□), CPZ(II) (◇), CPZ(I)-H′ (○) and CPZ(I)-H (⊠).

however were observed between CPZ(I)-H (2.47% w/w H_2O) and CPZ(I)-H′ (1.90% w/w H_2O) (Fig. 8).

Successful tableting also depends on the ability of the bonds within the tablet to withstand elastic recovery during decompression. The in-die tablet recovery was calculated and Young's modulus, E, was estimated from recovery data using the analysis of Dwivedi et al. (1992). Representative plots of the proportionality constant of Hooke's Law at a given porosity, E_p, as a function of tablet porosity are shown in Fig. 9. All tablets exhibited very low porosities. No differences were observed in the elastic recoveries of tablets of CPZ(I), CPZ (II), CPZ(I)-H′ and CPZ(I)-H during decompression.

In the previous work of Dwivedi et al. (1992), chlorpromazine hydrochloride lubricated with 0.5% magnesium stearate exhibited extensive recovery during decompression. An E value of 5.5 GPa was obtained, very similar to the microcrystalline celluloses (Avicel PH102 and Emcocel, 5.8 and 6.1 GPa, respectively) which makes strong tablets, and ibuprofen (5.9 GPa) which makes very weak tablets. Tablets made with 0.5% magnesium stearate laminated and capped, but the inclusion of 0.5% w/w talc enabled intact tablets to be made. The extent of elastic recovery during decompression was reduced and the E value was doubled.

Tablet strength was also evaluated. CPZ(II) did not form coherent tablets and therefore, it was not possible to measure the force of failure, F_f, in a diametral compression test. The F_f values of tablets of CPZ(I)-H and CPZ(I)-H′ were simi-

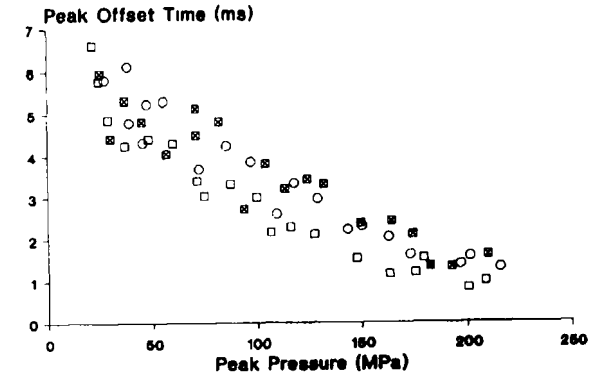


Fig. 8. Peak offset times of CPZ(I)-H′ (○), CPZ(I)-H (⊠) and CPZ(I) (□) with increasing compression pressures.

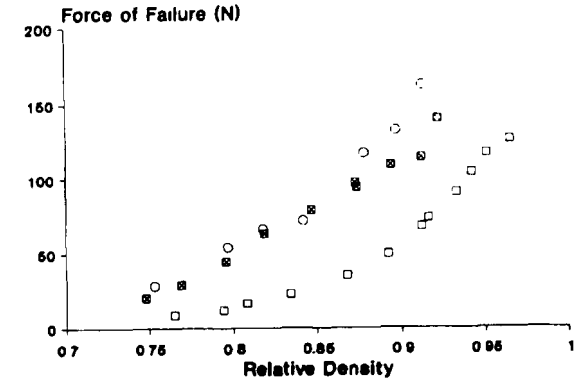


Fig. 10. Force of failure of tablets of CPZ(I)-H′ (○), CPZ(I)-H (⊠) and CPZ(I) (□).

lar to each other but consistently higher than CPZ(I) (Fig. 10).

The completely dehydrated lattice, CPZ(I), forms much stronger interparticulate bonds on compression than CPZ(II) and the tablets are able to withstand the stress of expansion during decompression. The presence of lattice water in CPZ(I)-H′ and CPZ(I)-H leads to a further increase in tablet strength which appear to be independent of the water content.

Conclusions

An unusual feature of the wet granulation process, using the water-ethanol mixture employed by Rhone-Poulenc, is that it leads to complete conversion to a stoichiometric hemihydrate without any signs of the original CPZ(II) starting material. On drying the material from the wet granulation process at 50°C, partially dehydrated cystals are formed. These crystals can be fully dehydrated to give the stable polymorphic form of CPZ. The crystal structures of the stable polymorph, the partially hydrated and the fully hydrated forms are the same with the exception of minor changes in lattice parameters. The powder pattern calculated using the method of Yvon et al. (1977) and the single crystal data of Klein and Conrad (1986) was identical to that of CPZ(I)-H. The lattice parameters of Klein and Conrad (1986) were used as the starting point in analyzing the effect of water vapor uptake on lattice expansion of CPZ(I).

Analysis of the tableting characteristics of CPZ(II) and its granules using an instrumented rotary press showed no appreciable differences in the extent of viscoplastic deformation during compression or in the elastic recovery of the compacts within the die during decompression. Hence differences in interparticulate bonding must be related to changes in the crystal lattice produced by wet granulation.

Acknowledgements

Financial support and a studentship to M.W.Y.W. from the Medical Research Council of Canada are gratefully acknowledged. We thank Rhone-Poulenc Pharma Inc. for the CPZ(II) and CPZ(I)-H′. The technical assistance of Dr L. Groat with the XRPD, Dr C. Fyfe with the solid-state NMR, Dr W. Riggs and Dr A. Szeitz in the GC analysis, and S. Dwivedi in the tableting studies are gratefully acknowledged.

References

Albert, A. and Serjeant, E.P., *The Determination of Ionization Constants A Laboratory Manual*, 3rd Edn, Chapman and Hall, London, 1984, p. 167

Appleman, D E and Evans, H T, Jr. U.S. Geological Survey Computer Distribution 20 *US National Technical Information Service* (1973) Doc. PB2-16188.

Borka, L., Review of crystal polymorphism of substances in the European Pharmacopoeia *Pharm Acta Helv*. 66 (1991) 16–22

Borka, L. and Haleblian, J K, Crystal polymorphism of pharmaceuticals. *Acta Pharm Jugosl*, 40 (1990) 71–94.

Chan, H.K and Doelker, E, Polymorphic transformation of some drugs under compression. *Drug Dev. Ind Pharm*, 11 (1985) 315–332

Cox, J S G, Woodard, G.D and McCrone, W.C, Solid-state chemistry of cromolyn sodium (disodium cromoglycate) *J Pharm Sci*, 60 (1971) 1458–1465

Dorignac-Calas, M R and Marsau, P, Structure cristalline du chlorhydrate de chloro-3-(dimethylamino-3′propyl)-10-phenothiazine *C R Acad Sci Paris*, 274 (1972) 1806–1809

Drickamer, H G, Pi electron systems at high pressure *Science*, 156 (1967) 1183–1189

Dwivedi, S.K., Oates, R J. and Mitchell, A.G., Peak offset times as an indication of stress relaxation during tableting on a rotary tablet press. *J Pharm Pharmacol*, 43 (1991) 673–678

Dwivedi, S.K., Oates, R.J and Mitchell, A G., Estimation of elastic recovery, work of decompression and Young's Modulus using a rotary tablet press *J Pharm Pharmacol*, 44 (1992) 459–464

Ibrahim, G, Pisano, F and Bruno, A, Polymorphism of phenylbutazone properties and compressional behavior of crystals *J Pharm Sci*, 66 (1977) 669–673

Kaneniwa, N. and Otsuka, M, Effect of grinding on the transformations of polymorphs of chloramphenicol palmitate *Chem Pharm Bull*, 33 (1985) 1660–1668

Klein, C L and Conrad III, J M., Structure of a new crystallographic form of chlorpromazine hydrochloride hemihydrate. *Acta Crystallogr.*, C42 (1986) 1083–1085.

Lefebvre, C, Guyot-Hermann, A.M, Draguet-Brughmans, M, Bouche, R and Guyot, J.C., Polymorphic transitions of carbamazepine during grinding and compression *Drug Dev Ind Pharm*, 12 (1986) 1913–1927

Lide, D.R, *CRC Handbook of Chemistry and Physics*, 72nd Edn, CRC Press, Boca Raton, FL, 1991, pp 5–101

Matsumoto, T., Kaneniwa, N., Higuchi, S. and Otsuka, M., Effects of temperature and pressure during compression on polymorphic transformation and crushing strength of chlorpropamide tablets. *J Pharm. Pharmacol*, 43 (1991) 74–78

Mitchell, A.G., The preparation and characterization of ferrous sulphate hydrates. *J Pharm. Pharmacol.*, 36 (1984) 506–510

National Physical Laboratory (Great Britain), *Notes on Applied Science No. 4 Measurement of Humidity*. HMSO, London, 1958.

Nogami, H., Nagai, T., Fukuoka, E. and Yotsuyanagi, T., Dissolution kinetics of bartital polymorphs *Chem Pharm Bull*, 17 (1969) 23–31.

Oates, R.J and Mitchell, A.G., Calculation of punch displacement and work of powder compaction on a rotary tablet press *J Pharm. Pharmacol*, 41 (1989) 517–523.

Oates, R.J. and Mitchell, A.G, Comparison of calculated and experimentally determined punch displacement on a rotary tablet press using both Manesty and IPT punches. *J Pharm Pharmacol.*, 42 (1990) 388–396

Otsuka, M. and Kaneniwa, N., Effect of seed crystals on solid-state transformation of polymorphs of chloramphenicol palmitate during grinding. *J Pharm Sci*, 75 (1986) 506–511

Otsuka, M, Matsumoto, T. and Kaneniwa, N., Effect of environmental temperature on polymorphic solid-state transformation of indomethacin during grinding *Chem Pharm Bull.*, 34 (1986) 1784–1793

Otsuka, M, Matsumoto, T. and Kaneniwa, N, Effects of the mechanical energy of multi-tableting compression on the polymorphic transformations of chlorpropamide. *J Pharm Pharmacol.*, 41 (1989) 665–669.

Pfeiffer, R.R., Yang, K.S. and Tucker, M.A., Crystal pseudopolymorphism of cephaloglycin and cephalexin. *J Pharm Sci.*, 59 (1970), 1809–1814

Summers, M P, Enever, R P and Carless, J.E., The influence of crystal form on the radial stress transmission characteristics of pharmaceutical materials. *J Pharm Pharmacol.*, 28 (1976) 89–99

Suryanarayanan, R and Mitchell, A.G., Phase transitions of calcium gluceptate *Int. J Pharm*, 32 (1986) 213–221.

Wall, G.M., Pharmaceutical applications of drug crystal studies *Pharm Manuf.*, February (1986) 33–42.

Winnike, R.A., Wurster, D E. and Guillory, J.K., A solid sampling device for use in batch solution calorimetry. *Thermochim. Acta*, 124 (1988) 99–108.

Wood, J.H., Syarto, J.E. and Letterman, H., Improved holder for intrinsic dissolution rate studies. *J. Pharm Sci*, 54 (1965) 1068.

Yvon, K, Jeitschko, W. and Parthe, E., *LAZY PULVERIX*, a computer program, for calculating X-ray and neutron diffraction powder patterns *J Appl Crystallogr*, 10 (1977) 73–74.